REMARKS

Claims 1, 3-11 and 13-19 are currently pending. Claims 7-10 and 13-19 are withdrawn from consideration. Claim 3 has been amended. Claims 2 and 12 have been cancelled. There being no issue of new matter, entry of the foregoing amendments is respectfully requested.

Claim Objections

The Examiner objected to claim 3 as being indefinite because it depends on claim 2 which has been cancelled. Claim 3 has been amended to be dependent on claim 1.

Claim Rejections 35 U.S.C §103

The Examiner rejected claims 1, 3-6 and 11 as being unpatentable over Reis et al. (WO 00/0170) in view of Romisch et al. (EP 0781558), Tsukada et al. (EP0781558) and Iqbal et al. and in view of Merck Manual regarding bacteraemia. The Examiner acknowledges that that Reis teaches that compound covered by the instant claims, (R)-2-(4-amidinophenylaminomethyl)-*1-methyl-5-[1-(carboxymethylamino)-1-pyrrolidinocarbonyl)-ethyl]-benzimidazole* is known as an antithrombic agent and not for treating sepsis, related disorders or bacteraemia. The Examiner asserts that Rominsch and Tsukada and Iqbal disclose the antothromic agents such as antithrombins have been useful for treatment of sepsis. Sepsis, the Examiner asserts is a stage of systemic inflammatory responsive syndrome, and often arises from bacteraemia and that intravascular coagulation are the common symptoms for sepsis. The Examiner also asserts that the cited art teaches that anticoagulant agents including those of antithrombic origin are expected to be useful for treating sepsis. The Examiner concludes that it would have been prima facie obvious for a person of ordinary skill in the art to employ the elected compound for the treatment of sepsis including those patients suffering from bacteremia.

Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness over the claims as presently amended, and request the rejection be withdrawn. The obviousness determination requires four kinds of factual inquiries:

(1) the scope and contents of the prior art;

(2) the differences between the prior art and the claims at issue;

(3) the level of ordinary skill in the pertinent art; and

(4) any objective indicia of success such as commercial success, long felt need, and copying.

KSR Int'l. Co., 127 S. Ct. at 1735 (citing *Graham v. John Deere Co.*, 383 US 1, 17-18 (1966)). The Supreme Court in *KSR* recognized that a showing of "teaching, suggestion, or motivation" to combine prior art could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 USC 103(a). *Id.* at 1741. The Supreme Court specifically stated that "it will be necessary . . . to determine whether there was an apparent reason to combine [or modify] the known elements [in the prior art] in the fashion claimed by the patent at issue. To facilitate review, this analysis *should be made explicit*." *Id.* at 1740 - 41 (emphasis added).

1. The scope and content of the prior art and differences between the prior art and the claimed invention

Applicant respectfully submits that the combination of cited references clearly do not provide a basis for a prima facie case of obviousness against the instant claims. The prior art combination of references coupled with the knowledge generally available at the time clearly would not have motivated someone skilled in the art to modify or combine the cited references to practice a *method for treating diseases selected from the group consisting of systemic inflammatory response syndrome (SIRS), sepsis and bacteranemia which comprises administering to a patient in need thereof a therapeutically effective amount of* (R)-2-(4-amidinophenylaminomethyl)-*1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole optionally in the form of the pharmaceutically acceptable acid addition salts thereof, and optionally in the form of the hydrates or solvates thereof.* For convenience the term "(R)-2-(4-

amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole optionally in the form of the pharmaceutically acceptable acid addition salts thereof, and optionally in the form of the hydrates or solvates thereof" will be referred to hereinafter as the "compound of formula (IIa)."

The Examiner asserts that Romisch and Tsukada and Iqbal disclose that antithrombotic agents are useful for treatment of sepsis. The Examiner broadly points to abstracts and the claims of Tsukada et al. and Romisch and the abstract of Iqbal et al. to support this premise. However, the cited references either individually or as a whole clearly fail to teach or suggests the use of the compound of formula (IIa) which has the property of inhibiting thrombin and factor X *directly*. The Examiner points to Romisch (Col. 1-2) and Iqbal (pages 111-115) which show that microvascular thrombosis and disseminated intravascular coagulation are common symptoms from sepsis, however a showing that coagulation is a common symptom of sepsis does not establish or support the premise that the instantly recited benzimidazole compound would be useful for treating sepsis. Likewise, the Examiner's arguments fail to provide a basis why someone skilled in the art would have an expectation of success of treating sepsis by administration of the recited benzimidazole compound.

2. The obviousness determination

As stated by the Examiner Reis et al fails to disclose the use of a benzimidizole compound according to formula (IIa) for the treatment of sepsis, or related disorders or bacteraemia. In the applicants view the references cited by the Examiner, Romisch, Tsukada and Iqbal either alone or in combination fails to teach all of the claim limitations of the instantly claimed invention. Specifically, **Rominsch and Tsukada and Iqbal individually or together do not teach the use of a benzimidizole compound according to formula IIa as in the instantly claimed invention which acts as a direct thrombin inhibitor for the treatment of sepsis.**

Tsukada, (EP application EP 0 781 558) teaches away from the method of the invention as instantly claimed. Tsukada describes the use of heparin cofactor II in the potential treatment of infectious disease, particularly sepsis and a variety of other diseases accompanied by thromboses. Tsukada discloses heparin cofactor II as a plasma glycoprotein which is known to inhibit thrombin *mainly in the presence of dermatan sulphate and/or a large quantity of heparin.* The compound according to formula (IIa) has been evaluated in an animal model using purified LPS (Lipopolysaccharide) in order to simulate an inflammatory response (see Example 2 of the specification, page 36). This experimental model seeks to reflect the systemic inflammatory response syndrome which can be related to a variety of stimuli rather than an infectious model mimicking the particular aspects of sepsis, i.e. the infectious disease related aspects. Importantly, the claimed compound was shown to reduce organ damage in this model so that it can be concluded that the use of the compound of formula (IIa) is not related to infectious agents as in sepsis but to SIRS in general. Therefore, the results with the compound of formula (IIa) in a model without an infectious agent would not have been expected. While Tsukada teaches a role of heparin in the treatment of sepsis there is no teaching or suggestion to use a benzimidazole compound such as a compound according to formula (IIa) claimed which acts a direct inhibitor compound for the treatment of sepsis.

As compared to heparin cofactor II, the compound according to formula (IIa) is a *direct inhibitor* of thrombin and factor Xa. There is no interaction with dermatan sulphate or heparin. Consequently, someone skilled in the art would not have any motivation to use the claimed compound in the instant claims for the treatment of sepsis.

The compound of formula (IIa) has shown efficacy in a model of inflammation clearly distinct from a sepsis, i.e. infectious disease model. Furthermore, the effect is related to its *direct* activity against thrombin and factor Xa and is not related to either effects on inflammatory cytokines or interaction with heparin or dermatan sulphate.

Romisch clearly teaches away from the method of the invention because it describes the use of antithrombin for the treatment of inflammatory processes being accompanied by

an increased distribution of cytokines and/or tissue factor. The reference highlights the anti-inflammatory properties of antithrombin which are *distinct* from its anti-thrombin and anti-clotting capability (See Col. 1, line 55-57). The reference teaches that Antithrombin III is not acting as an anticoagulant but may affect the signalling mechanism for regulation of the proinflammatory cytokines (See Col. 2, lines 17-20). This rationale is consistent with the prevailing knowledge and expectations in the art that an increase of inflammatory mediators is the primary reason for organ dysfunction and failure in sepsis. The compound according to formula (IIa) the invention is a pure anticoagulant inhibiting thrombin and factor Xa directly. Therefore, in contrast to the cited references a compound according to formula (IIa) would be expected to have no direct anti-inflammatory effects. Consequently, this reference teaches away from employing a method the employs compounds which have the property of inhibiting thrombin and factor X directly.

- *Iqbal et al.* (Expert Opinions Emerging Drugs 2002, 7, 111-139) also teaches away from the method of the claimed invention. Iqbal describes the use of anticoagulants in the treatment of severe sepsis. The reference discusses sepsis as an inflammatory response to a microbial agent and highlights the role of bacteria in sepsis, particularly with regard to the differences between gram-negative and gram-positive sepsis and respective predisposing factors. The reference highlights the role of the immune system for the response to infection and proposes various inflammatory mediators as targets for sepsis treatment. The reference also describes the role of activated coagulation in severe sepsis. The reference proposes the use of anticoagulants in the treatment of sepsis. The proposal is based on the rationale that since intravascular thrombi and disseminated intravascular coagulation in humans with severe sepsis is present that the coagulation system is activated. The reference describes anticoagulants which are currently in use or in development as potential treatments for severe sepsis and describe the results of three clinical development programmes for activated protein C, antithrombin and TFPI. Of the three the only successful one was activated protein C (APC) programme. For all three, an additional anti-inflammatory mechanism has been proposed which is also reflected in

this overview which gives thorough details how APC interactions with inflammation via the EPC-receptor.

At point eight of the Office Action the Examiner argues that one can not show non-obviousness by attacking references individually where the rejections are based on combinations of references and that the references as a whole show the usefulness of various antithrombic agents for treatment of sepsis, regardless of the underlying biochemical mechanism of those antianthrombic agents. Applicant respectfully submits that the Examiner has failed to show how the how the references as a whole teach the usefulness of antithrombics such as instantly claimed that act as *direct* antithrombics for treatment of sepsis. Clearly, the prevailing thought in these references was that successful compounds for use in the treatment if sepsis would operate through an indirect and immune mechanism.

The Examiner asserts that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiment. Applicant submits that in a proper reading of the cited references as a whole, (i.e. supporting antithrombic agents that operated in an indirect manner) that the compound according to formula II would not be considered a suitable compound for the treatment of sepsis and that there would have been no expectation of success associated with its use.

Conclusion

It is clear that the claims 1, 3-6 and 11 are not obvious over Reis et al. (WO 00/0170) in view of Romisch et al. (EP 0781558), Tsukada et al. (EP0781558) and Iqbal et al. and in view of Merck Manual regarding bacteraemia and these references fail to teach the use of a compound according the formula II for the treatment of sepsis. Furthermore, there is no reasonable expectation of success in practicing the claimed invention for the foregoing reasons. As the rejection under 35 USC § 103(a) is improper, Applicants respectfully request that it be withdrawn.

Authorization for payment of fees for a three month extension of time for reply to the Office Action is hereby given. It not believed that any other fees are required beyond those that may otherwise be provided for in accompanying documents. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. §1.136(a) and any fees required therefore are hereby authorized to be charged to our Deposit Account No. 02-2955.

If any points remain at issue which can best be resolved by way of a telephonic or personal interview, the Examiner is kindly requested to contact the undersigned attorney at the local telephone number listed below

Respectfully submitted,

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